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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/214,251	03/10/99	KING D	CARP-0067

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EXAMINER	
HELMS,L	
ART UNIT	**PAPER NUMBER**
1642	5

DATE MAILED: 11/17/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/214,251	King et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-10* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-10* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1, 6, and 9 have been amended.

Claims 1-10 are pending and under examination.

Specification

1. The specification is objected to for it lacks a Brief Description of The Drawings.

2. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

3. The specification is objected to for the first line of the specification should state that this application is the 371 U.S. national-phase application of PCT international Application No. GB97/03400, filed 12/10/97..

4. The use of the apparent trademarks "Streamline A"" (page 15, line 7) for example, has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1 is indefinite for reciting "modified" for it is not known what modifications are allowed or contemplated. Is the only modification the addition of the polymer or are other modifications intended? As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

b. Claims 4 and 5 are indefinite for reciting "derivatives thereof". The claims are indefinite for reciting "derivative" as the exact meaning of the word is not known. The term "derivative" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the molecules are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Accordingly, it is impossible to determine the metes and bounds of the claimed invention.

c. Claims 3, 4, and 5 are indefinite for reciting "optionally" for it is not clear what is meant by the term. What options are encompassed by the term? Accordingly, it is impossible to determine the metes and bounds of the claimed invention.

d. Claims 3, 4, and 5 are indefinite as being structured as an improper Markush claims. (See MPEP 2173.05(h)). It is not clear if, for example, in claim 3 the phrase "optionally substituted" is intended to modify the term straight, or branched chain polyalkylene, or polyalkenylene, etc. Similarly, it is unclear if the phrase "optionally substituted" in claim 5 is intended to modify the term strait, or branched chain poly(ethylene glycol), or poly(propylene glycol), etc. Furthermore, it is unclear if in claim 5 the phrase "polymer" is modifying the term methoxy(polyethylene glycol) and derivatives thereof, or just derivatives thereof. Proper Markush claims are in the format of "X is selected from a group consisting of A, B, C, and D," or "the X is A, B, C or D".

e. Claim 6 is indefinite for reciting "associated" for it is not known what is meant by the term. Is the term intended to mean the V_H and V_L dimers are in the same test tube, aggregated, or dimerized by ionic or hydrogen bonds? As written, it is impossible to determine the metes and bounds of the claimed invention.

f. Claim 7 is indefinite for reciting "and/or"for it is not clear what is meant by the term. Is the term intended to mean that the V_H and the V_L domain is attached to the C-terminal amino acid or does the term mean the V_H or the V_L domain is attached to the C-terminal amino acid Accordingly, it is impossible to determine the metes and bounds of the claimed invention.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a monovalent antibody together with one or more pharmaceutically acceptable excipients, diluent, or carriers, does not reasonably provide enablement for a pharmaceutical composition comprising a monovalent antibody together with one or more pharmaceutically acceptable excipients, diluent, or carriers . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. .

a. The claim is drawn to a pharmaceutical composition comprising an antibody. Enablement of a "pharmaceutical composition" is considered to rest on a teaching of in vivo administration for purposes consistent with the intended use disclosed in the specification. The disclosed intended use for the claimed pharmaceutical composition is for the treatment of many diseases (see page 11, lines 21-31) such as infections, inflammation, sickle cell anaemia, etc.. Thus, the nature of the invention is an immunogenic/therapeutic composition used in the treatment of infectious, graft-versus-host, and metabolic/idiopathic disease.

b. Although the specification discloses the claimed composition, and general methods for formulating compositions in pharmaceutically acceptable carriers, there is insufficient guidance

which would enable one skilled in the art to use the claimed compositions for their intended purpose, viz., for the treatment against disease.

c. At the time the invention was made, pharmaceutical compositions comprising the claimed antibodies were not routinely used for the treatment of a wide variety of diseases. The specification lacks guidance by way of general methods or working examples which teach an amount of the polypeptide which would be used for this purpose. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art, such as immunotherapy of disease. Accordingly, there is no objective basis upon which the skilled artisan would reasonably be able to determine or predict an amount of the claimed composition effective for its intended use. Therefore, undue experimentation would be required to make and use the invention.

d. Amending the claims by removing the term "pharmaceutical" before composition would obviate this rejection.

9. Claims 1-7 and 9-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antigen binding antibody fragments, Fab and Fab', does not reasonably provide enablement for antibody fragments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. The claims are drawn to "antibody fragment" of antibodies. The specification discloses "antibody fragment" as "antibody fragments of the invention will in general be capable of selectively binding to an antigen" (see page 4 lines 6-7). The specification is silent as to what structural features are necessary for antibody fragments selectively binding to the antigen.

c. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make derivatives of the claimed antibodies commensurate in scope with the claims, since the specification gives insufficient guidance on or exemplification of how to make all of these types of modified proteins. Antibody fragments, as broadly drawn, read on antibodies that have been subjected to deletions, truncations as well as substitutions. However, applicant has not enabled all of these types of modified proteins because it has not been shown that these modified proteins are capable of functioning as that which is being disclosed.

d. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al. J of Cell Bio. 111:2129-2138, (1990)). In

transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al., Molecular and Cellular Biology 8:1247-1252 (1988)).

e. In addition, it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that all antibodies as defined by the claims which may contain altered CDRs from the heavy and light chain variable regions of an antibody have the required binding function. The specification provides inadequate direction or guidance regarding how to produce all antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino

acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

f. Similarly it has been shown that a glycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies. See Tao et al., The Journal of Immunology, 143:2595-2601 (1989). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

g. Further, the specification fails to teach what deletions, truncations, substitutions and mutations of the antibody would be tolerated that will allow the antibody to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding (including antibody CDR regions) will certainly be among the most conserved (see Bowie et al (Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make all possible antibody fragments that are necessary for proper function including antigen binding specific for the claimed invention.

h. Therefore, in view of the speculative nature of the invention, the lack of predictability of the prior art, the breadth of the claims, insufficient teachings and guidance in the specification, and insufficient working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed using any antibody fragment.

I. Removing the term "antibody fragment" or defining precisely what is meant by the limitation in a manner fully supported by the specification that is limiting claims to antigen binding fragments, Fab, and Fab' may be sufficient to obviate this rejection.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Pedley et al (Br. J. Cancer, Vol. 70, pp 1126-30, 1994).

a. The claims are drawn to a modified monovalent antibody fragment comprising a antibody fragment and at least one polymer molecule covalently linked in that each cysteine residue located outside the variable domain is either linked through its sulphur to the polymer or is disulfide linked with a second cysteine residue located in the fragment provided that at least one of said cysteine residues is linked to a polymer molecule. Further embodiments are linkage of one, two, or three polymer molecules through one, two, or three cysteine residues, wherein the polymer is a straight or branch chain of polyalkylene, polyalkenylene, or polyoxyalkylene or branched or unbranched polysaccharide, or the polymer is a straight or branch chain of poly(ethylene glycol), poly(propylene glycol), or poly(vinyl alcohol) and derivatives thereof, or methoxy(polyethylene glycol) and derivatives thereof. The antibody fragment which the variable region is monomeric and comprises the immunoglobulin heavy or light chain domain or is

dimeric, wherein each VH and/or VL domain is covalently attached to the C-terminal amino acid to at least one other antibody domain or fragment thereof, where the fragment is a Fab or Fab', wherein the antibody fragment is covalently attached to one or more effector or reporter molecules, and a pharmaceutical composition of the antibody fragment with a pharmaceutically acceptable carrier.

b. Pedley et al teach the covalent attachment of poly(ethylene glycol) (PEG) to an antibody, a Fab fragment, and a Fab' fragment of anti-CEA (see abstract). Pedley et al modified the cysteine residues outside the variable region of the antibody fragments with PEG producing two polymer molecules per antibody (see page 1128, right side first paragraph). Pedley et al also teach the radiolabelling of the PEG-modified antibodies (see page 1127, left column, Radiolabelling) and the PEG-modified antibody fragment in PBS (see page 1127 left column first full paragraph). Since claim 5 recites the polymer is methoxy(polyethylene glycol) and derivatives thereof, the claim is being interpreted as reading on poly(ethylene glycol). The phrase "pharmaceutical composition" is given no weight (see 112, 2nd paragraph rejection above) because it is being interpreted as an intended use of the product. Thus, the reference of Pedley et al meets the limitations of the claims.

Conclusions

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879